INVESTIGATION OF NONINVASIVE MUSCLE PH AND OXYGEN SATURATION DURING UNCONTROLLED HEMORRHAGE AND RESUSCITATION IN SWINE

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ABSTRACT   This study evaluated noninvasively determined muscle pH (pHm) and muscle oxygen saturation (SmO$_2$) in a swine shock model that used uncontrolled hemorrhage and restricted volume resuscitation. Anesthetized 40-kg female swine underwent hemorrhage until 24 mL/kg of blood was removed (n   26), followed by transection of the spleen, causing uncontrolled hemorrhage throughout the remainder of the protocol. After 15 min, 15 mL/kg of resuscitation fluid (Hextend, fresh-frozen plasma or platelets) was given for 30 min. Arterial and venous blood gases were measured at baseline, shock, end of resuscitation, and end of the study (death or 5 h), along with lactate and base excess. In addition, seven animals underwent a sham procedure. Spectra were collected continuously from the posterior thigh using a prototype CareGuide 1100 Oximeter, and pHm and SmO$_2$ were calculated from the spectra. A two-factor analysis of variance with repeated measures followed by Tukey *post hoc* comparisons was used to compare experimental factors. It was shown that, for both pH and SO$_2$, venous and muscle values were similar to each other at the end of the resuscitation period and at the end of the study for both surviving and nonsurviving animals. pH and SO$_2$, venous and muscle, significantly declined as a result of bleeding, but lactate and base excess did not show significant changes during this period. Noninvasive pHm and SmO$_2$ tracked the adequacy of resuscitation in real time, indicating at the time all of the fluid was delivered, which animals would live and which would die. The results of this swine study indicate that further evaluation on trauma patients is warranted.

KEYWORDS   Hemorrhage, fluid resuscitation, NIRS, noninvasive monitoring, acidosis, oxygen debt

INTRODUCTION

Despite a number of advances in recent years, hemorrhage is still responsible for high mortality in both civilian and military settings (1) and is the leading cause of preventable death from traumatic injuries (2). Hemorrhage from the periphery is well addressed by improved use of tourniquets (3), so strategies for reducing mortality have shifted to addressing uncontrolled bleeding of the torso. The military has adapted resuscitation strategies with the goal of stabilizing the patient as quickly as possible and providing only interventions necessary to control hemorrhage and "establish a survivable physiological status" (4). This care is generally provided near the point of injury and during transport to the hospital, where more definitive and complex surgeries can be carried out (2, 5).

Often, in the early care of these patients, blood pressure is kept low for fear that high pressure may "pop a clot" that is helping to control the bleeding. However, one of the risks of low blood pressure is that there may not be sufficient perfusion of end organs (4). In a hospital setting, end-organ perfusion would be assessed with repeated blood sampling to measure lactate or base excess (BE), determinants of acidosis. However, this is not possible in the prehospital environment, where blood sampling is challenging and laboratory analysis equipment is unavailable. Instead, an easy-to-use continuous noninvasive monitor would be a more appropriate method for assessing acidosis and whether treatment was adequate to perfuse all organs. Noninvasive patient monitors can be easily and quickly placed by first responders who generally are not trained to collect blood samples. Values are obtained immediately and continuously, freeing the responder to take care of the patient. Noninvasive patient monitors are commercially available to assess tissue oxygen saturation (StO$_2$) as a marker of end-organ perfusion. Swine and human studies have demonstrated that noninvasive continuous StO$_2$ monitoring can track the adequacy of oxygen delivery during hemorrhagic shock (6, 7), the need for massive transfusions (8), and the adequacy of resuscitation (9, 10).

Recently, a new monitor has become commercially available that noninvasively measures muscle pH (pHm), a measure of acidosis, in combination with muscle oxygen saturation (SmO$_2$) (11). This swine study is the first to evaluate the noninvasive pHm sensor in the setting of uncontrolled hemorrhage with restricted volume resuscitation. Noninvasive pHm and SmO$_2$ were compared with venous and arterial pH, SO$_2$, lactate, and BE. We further investigated whether pHm and SmO$_2$ were indicative of animal survival during the period when resuscitation fluid was administered; this assessment is the first step in

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determining if these parameters might, in the future, be useful for real-time guidance of resuscitation from hemorrhagic shock.

MATERIALS AND METHODS

Surgical instrumentation

This study was conducted in a facility accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care International and approved by the Institutional Animal Care and Use Committee of the US Army Institute of Surgical Research (Fort Sam Houston, Tex). This study has been conducted in compliance with the Animal Welfare Act, the implementing Animal Welfare Regulations, and the principles of the Guide for the Care and Use of Laboratory Animals. The experimental procedure has been described in detail in a previous publication (12), is summarized schematically in Figure 1, and is summarized here.

Yorkshire cross female pigs weighing 39.1 ± 0.5 kg (Midwest Swine Research, Gibbon, Minn) were used for the study. The pigs were fasted 12 to 18 h before surgery with water available *ad libitum*. Before surgery, the pigs were injected with glycopyrrolate (Robinul, 0.01 mg/kg; Baxter Healthcare, Deerfield, Ill) and tiletamine zolazepam (Telazol, 8 mg/kg; Wyeth, Fort Dodge, Iowa) in tramuscularly, for saliva secretion control and sedation, respectively. Anesthesia was induced via a facemask with approximately 5% isoflurane (Forane; Baxter Healthcare) in 100% oxygen and then maintained during surgical instrumentation

with 1% to 3% isoflurane in 30% oxygen in air using a ventilator and monitor (Apollo; Draeger Medical, Telford, Pa). Animals were placed in the supine position, and electrocardiogram electrodes were attached to monitor the heart rate (HR). Ventilation was adjusted to maintain an end tidal PCO$_2$ of approximately 40 mmHg. Core temperature was maintained between 37°C and 39°C.

A pressure transducer tipped catheter (Mikro Tip; Millar Instruments, Inc, Houston, Tex) was placed in the carotid artery for blood pressure monitoring. A catheter was placed in the jugular vein for blood sampling. Additional catheters were placed in the left femoral artery and vein for arterial hemorrhage, blood sampling, and intravenous infusion of the resuscitation fluid. A Swan Ganz catheter was advanced into the pulmonary artery via a jugular vein for measurement of cardiac output. A laparotomy was performed to access the spleen. Suction tubes with perforated tips were placed in the peritoneal cavity to collect blood from the injured spleen. The animals were not heparinized, and catheters were kept patent with a slow continuous infusion of nonheparinized saline.

Experimental procedure

After the instrumentation was completed and the mean arterial blood pressure (MAP) stabilized, a 10 min baseline period began and hemodynamic measurements were recorded. All data from the analog and RS 232 signals were collected on a data acquisition instrumentation rack/biomedical data recorder and physiological data recorder program (Dynamic Research Evaluation Workstation DREW, US Army Institute of Surgical Research, San Antonio, Tex). After blood draws for baseline measurements (Baseline), a controlled hemorrhage was performed by removing 24 mL/kg blood at a rate of 100 mL/min using a custom servocontrolled computerized pump program as previously described (12); this was typically completed in 15 min. After the controlled hemorrhage, a splenic injury was made by transecting the spleen along the long axis, offset 1 cm from the midline to avoid large vessels, and the uncontrolled hemorrhage volume was measured continuously by suctioning shed blood into canisters placed on a balance. Preliminary studies indicated that the majority of splenic bleeding is completed in 15 min after injury, and this is comparable to the time when a combat medic would be expected to begin treatment of an injured casualty on the battlefield (12). A blood sample was collected at the end of the initial 15 min blood loss from the splenic injury (Shock).

Resuscitation fluid (15 mL/kg of Hextend, fresh frozen plasma (FFP), cryoprecipitate and FFP, or platelets and FFP) was provided at a rate of 1 mL/kg per min; typically, all fluid was delivered within 30 min. Hypotensive resuscitation was performed such that the pump was turned off if MAP reached 67 mmHg and turned on when MAP reached 63 mmHg (Resuscitation).

Animals were monitored for 5 h after the splenic injury or until death (End), and no additional fluid was given. During this period, blood pressure was not manipulated. In addition to the baseline blood sample, arterial and venous samples were drawn for analysis at 15 (Shock), 60 (Resuscitation), and 300 min after injury or at death if the animal did not survive. Arterial and venous oxygen saturation and pH were determined at each time point (COBAS b 221 blood gas system; Dade Behring, Deerfield, Ill).

This article describes a subset of animals (n = 38) from a larger parent study that is described more fully in the online supplement (see Supplemental Digital Content 1 at http://links.lww.com/SHK/A209). Treatments for the animals used in the analysis are summarized in Table 1. The data from five of the 38 animals were excluded because of errors detected in the signals received from the CareGuide device, indicating that poor contact was made on the swine hind limb. A total of seven animals underwent a sham procedure where all of the surgical steps were carried out, except the spleen laceration. No hemorrhage was performed, and no resuscitation fluid was provided. A positive control group included a splenectomy (i.e., definitive surgical hemostasis via splenic vessel ligation, followed by removal of the spleen) performed after the 15 min blood sample. Swine FFP (15 mL/kg) was administered after removal of the spleen. In the remaining animals, the injured spleen was left in place and the pigs were resuscitated with one of four test solutions: Hextend, FFP, swine plateletpheresis platelets equivalent to a standard six pack with the remaining volume made up with FFP, or swine cryoprecipitate with the remaining volume made up with FFP.

Near-infrared spectroscopy

Near infrared spectroscopy (NIRS) data were collected continuously from the biceps femoris muscle with a prototype version of the CareGuide Oximeter 1100 (Reflectance Medical Inc, Westborough, Mass). The CareGuide Oximeter uses two different source detector separation distances to correct the spectra for interference from skin and fat. Incident light is produced by a broad band NIR LED light source that illuminates the tissue over the range of 700 to 900 nm. The sensor has a chip scale spectrophotometer parallel to a row of light sources spaced at different distances (6 – 45 mm) from the spectrometer. One light source, placed 6 mm from the spectrometer, collects light reflected from near the tissue surface, capturing the spectrum associated with the skin pigment. A series of six light sources spaced 5 mm apart and 20 to 45 mm from the spectrometer are used to

Swine Protocol   **Blood Samples**

- **Instrument Pig**

- **Baseline** after 10min stabilization

- **Controlled Hemorrhage** (24mL/kg removed at a rate of 100mL/min taking ~15min)

- **Spleen Injury** (uncontrolled hemorrhage)

- **Shock** after 15min uncontrolled bleeding

- **Resuscitation** (15mg/kg given at a rate of 1mL/kg/min taking ~30min)

- **Resuscitation** 45min after shock sample

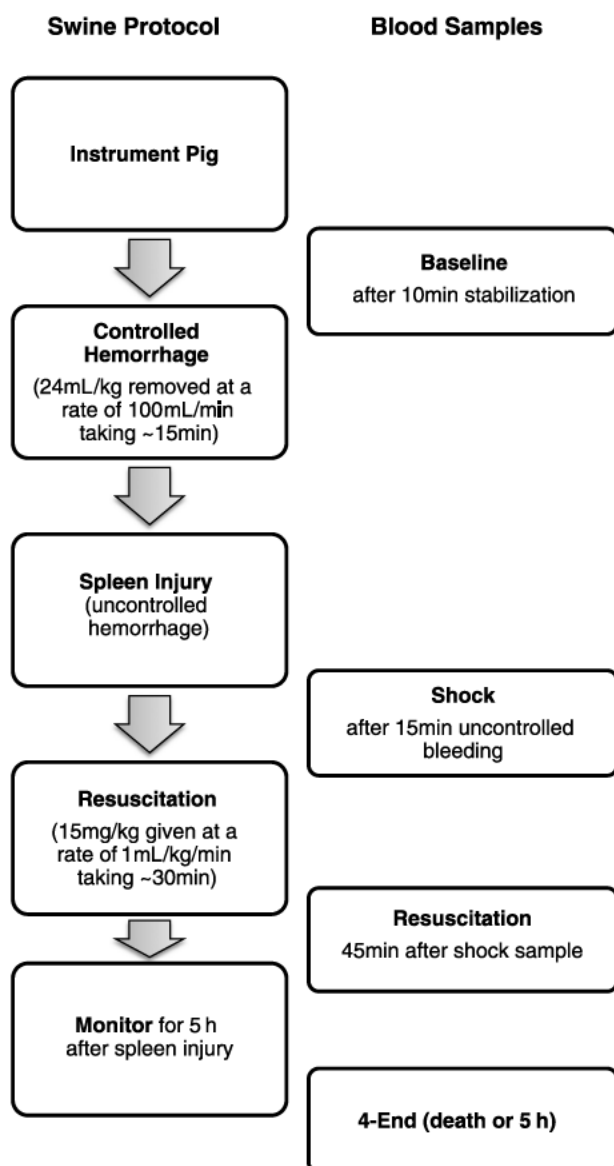- **Monitor** for 5 h after spleen injury

- **4-End (death or 5 h)**

Fig. 1. **Flow diagram of experimental procedure and timing of blood samples.**

TABLE 1. **Resuscitation treatment and outcome (number per group)**

Group	Lived (n)	Died (n)	Total (n)
Sham	7	0	7
Treated			
Splenectomy + FFP (positive control)	4	1*	5
Hextend	0	4	4
FFP	2	3	5
Platelets + FFP	2	3	5
Cryoprecipitate + FFP	5	2	7
Totals for treated groups	13	13	26

*The ligature slipped in one animal and that animal died.
FFP swine fresh-frozen plasma.

illuminate the muscle. The sensor automatically selects the light source that is at an appropriate distance to capture light reflected back from the muscle. Thicker fat layers require longer separations to increase the depth of penetration into the tissue. The muscle spectra are corrected by mathematically removing the spectral information from the skin pigment, and SmO_2 is calculated from the isolated muscle spectrum. Muscle pH was calculated from the same spectra using the algorithm contained in the Mobile CareGuide 3100 (11).

Data analysis and statistics

Retrospectively, the animals were divided into three groups: sham, survi vors, and nonsurvivors. Survivors were the animals that were alive for 5 h after splenic injury. Because there was no difference in survival as a function of type of resuscitation fluid, most likely because of lack of power with the subgroups, the fluid type was not considered a factor for this analysis. The results on the differences because of the fluid types will be reported elsewhere.

Noninvasive SmO_2 and pHm were collected continuously, updated approxi mately every 30 s (33 ± 0.4; range, 15 85 s). For the hemodynamic variables and the NIRS parameters, values at 5 min intervals of the responses during con trolled hemorrhage, the shock period, and the resuscitation period to 60 min were reported. Total peripheral resistance, oxygen delivery, and oxygen extraction ratio (OER) were calculated using standard equations (12).

A two way repeated measures analysis of variance with a Tukey *post hoc* test for pairwise multiple comparisons was performed to assess the blood, hemodynamic, and noninvasive parameters to distinguish those animals that survived and those that died after resuscitation. A Kaplan Meier log rank test was used to assess survival. Data were analyzed with SigmaPlot Version 12.0 (Systat Software, Chicago, Ill). Significance was determined at $P < 0.05$. Values are reported and plotted as mean ± SE.

RESULTS

Hemodynamics

A total of seven animals underwent the sham protocol, and 26 swine completed the shock portion of the study. All of the sham animals survived, but only half (13 of 26) of the animals that were bled survived the full 5 h (Table 1). Figure 2 sum marizes the systemic hemodynamic parameters: systolic blood pressure (SBP), cumulative total blood loss including the con trolled and uncontrolled hemorrhage volumes, resuscitation vol ume, HR, central venous pressure (CVP), cardiac output (CO), and total peripheral resistance (TPR) for the sham group, the survivors (lived), and the nonsurvivors (died) at four specific time points during the study. Hemodynamics were unchanged from baseline for animals in the sham group, validating the stability of the animal model.

Hemorrhage lowered the SBP, CVP, and CO equivalently for pigs that lived and died. Heart rate and TPR increased during the hemorrhage period. Blood loss at the end of the shock period was slightly but significantly greater for the nonsurvivors compared with the survivors and continued to increase after resuscitation. The final total blood loss in the survivors was 34 ± 1 mL/kg

(48% of the estimated blood volume) and 55 ± 2 mL/kg (79% of the estimated blood volume) in the nonsurvivors. The average survival time for the nonsurvivors was 105 ± 8 min, which was significantly different ($P < 0.001$) from the 300 ± 0 min for the sham and survivors. All nonsurvivors died by 180 min. A Kaplan-Meier survival curve is provided in the supple mental data section (see Supplemental Digital Content 1 at http://links.lww.com/SHK/A209).
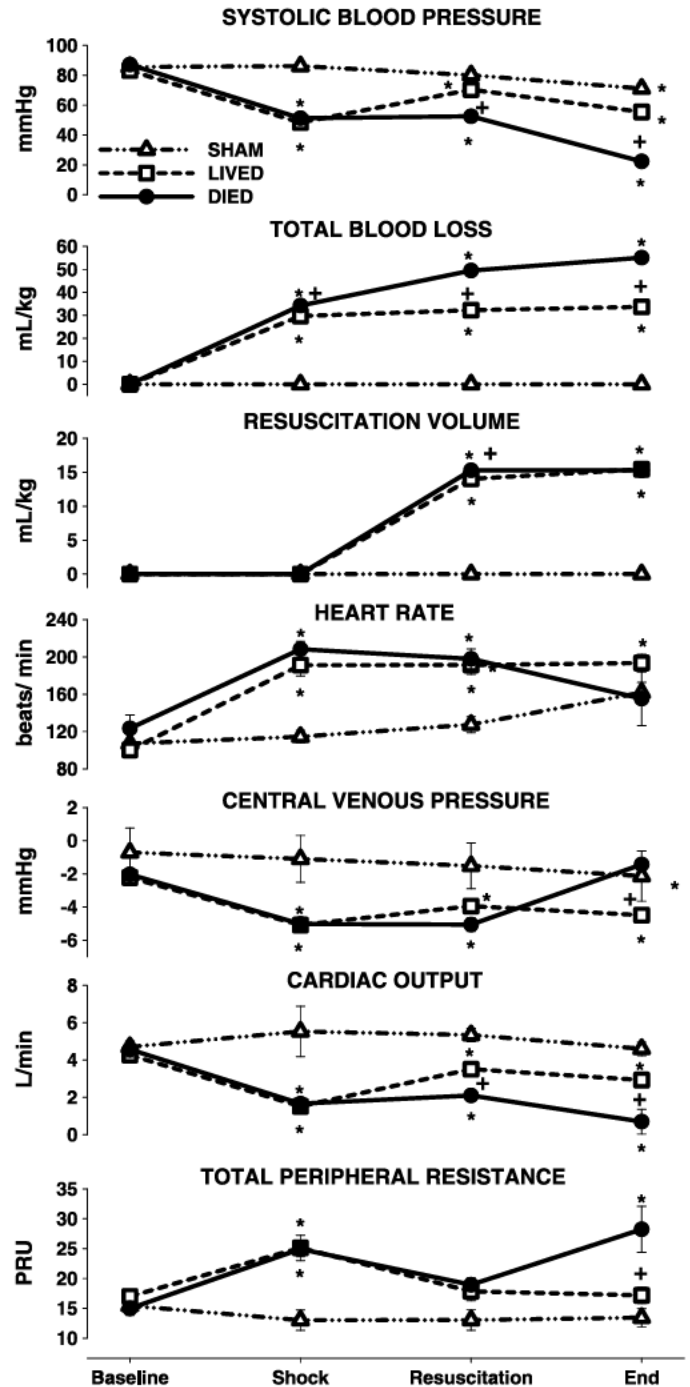

FIG. 2. **Average systolic blood pressure, total blood loss, resuscitation volume, heart rate, central venous pressure, cardiac output, and total peripheral resistance for sham (Δ), survivors (lived) (□), and nonsurvivors (died) (•). Mean ± SE. Time for last nonsurvivor value was actually time of death. *$P < 0.05$ compared with baseline. +$P < 0.05$ between Lived and Died at specified time points.**

Resuscitation volume was slightly lower in surviving pigs compared with nonsurvivors at 60 min because of the splenectomy procedure delaying the onset of resuscitation, but equivalent volumes were eventually received by both groups. At the end of resuscitation (60 min), SBP for survivors was similar to that of the shams but significantly different from pigs that died. Heart rate remained elevated through resuscitation and the remainder of the protocol for all nonsham animals. Cardiac output increased significantly in survivors compared with the nonsurvivors in response to resuscitation and at the end but remained lower than baseline and the sham group throughout. Total peripheral resistance returned to baseline/sham levels in response to resuscitation in both groups but increased at the end for the nonsurviving pigs.

Comparison of SmO$_2$ with invasive determination of oxygenation

Figure 3 examines the comparison of NIRS noninvasive SmO$_2$ with invasively determined oxygenation parameters: arterial (SaO$_2$) and venous (SvO$_2$) oxygen saturation, arterial (CaO$_2$) and venous (CvO$_2$) oxygen content, and the OER for animals in the sham, lived, and died groups at the four time points. The SaO$_2$ was near 100% for sham, lived, and died and did not change significantly during the protocol. Average SvO$_2$ at baseline was 73% ± 3% for survivors and 71% ± 2% for nonsurvivors and declined to under 30% as a result of hemorrhage. At the end of fluid resuscitation, surviving animals had a significant increase in SvO$_2$ compared with nonsurvivors ($P < 0.001$) although not to baseline levels. At the end of the study, SvO$_2$ was still low for survivors (34% ± 7%) but not as low as for nonsurvivors at the time of death (13% ± 1%). The SmO$_2$ decreased as a result of hemorrhage for both survivors and nonsurvivors, whereas the values for sham animals were unchanged. Average SmO$_2$ was lower at baseline than SvO$_2$, 42% ± 3% for animals that lived and 42% ± 5% for those that died. The SmO$_2$ was not significantly ($P = 0.106$) different from the SvO$_2$ at shock, resuscitation, and the end of the study for both survivors (SvO$_2$: 28% ± 4%, 43% ± 3%, and 34% ± 7%; SmO$_2$: 23% ± 3%, 36% ± 3%, and 40% ± 4% for shock, resuscitation, and end, respectively) and nonsurvivors (SvO$_2$: 23% ± 2%, 21% ± 2%, and 13% ± 1%; SmO$_2$: 25% ± 5%, 24% ± 5%, and 18% ± 3% for shock, resuscitation, and end, respectively). The arterial (CaO$_2$) and venous (CvO$_2$) were unchanged in the shams. There was no change in CaO$_2$ in either survivors or nonsurvivors at the end of shock. After resuscitation, CaO$_2$ was reduced because of hemodilution and continued blood loss, with that of nonsurvivors significantly lower than that of survivors. The CvO$_2$ was reduced significantly in response to shock to an equal extent in both survivors and nonsurvivors. The CvO$_2$ continued to fall in the nonsurviving group after resuscitation to significantly lower levels than surviving animals. The OER is a sensitive indicator of how well the tissue is being perfused. The levels started out low at baseline (30% ± 2%) and remained stable throughout in shams. In response to shock, the OER rose significantly higher in the nonsurvivor group compared with the survivors and stayed high in the nonsurviving animals after resuscitation. Oxygen extraction ratio fell initially in the surviving pigs in response to resuscitation but increased again at the end.
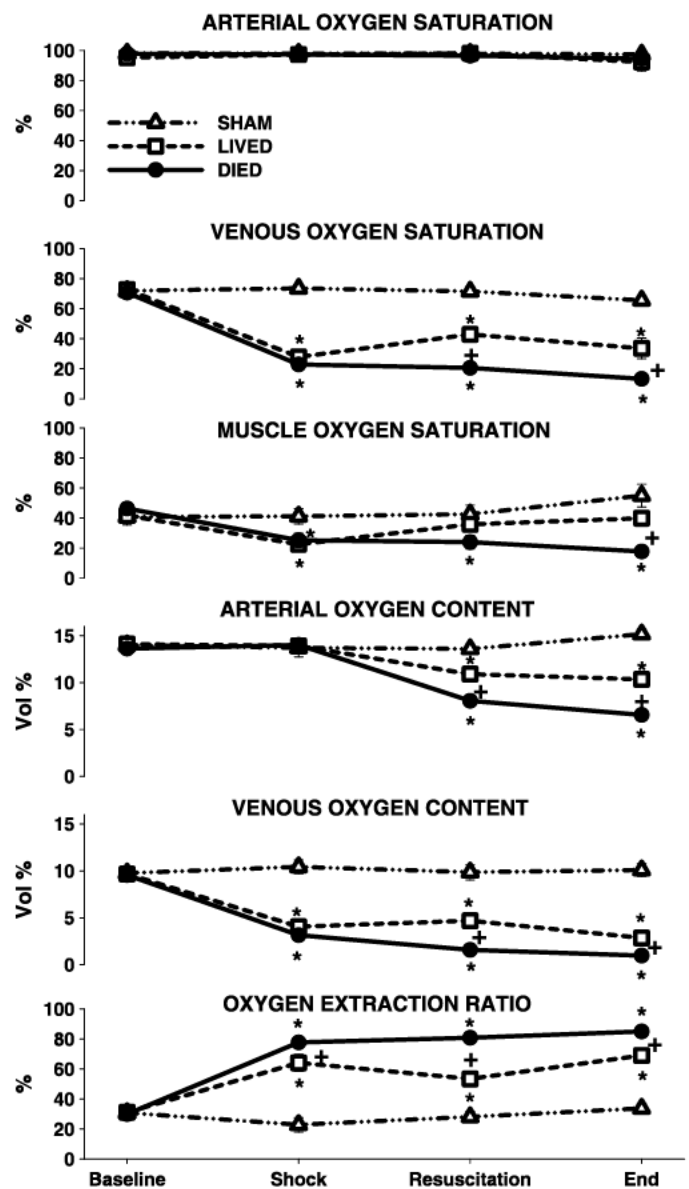

FIG. 3. Average arterial, venous, and noninvasive muscle oxygen saturation, arterial and venous oxygen contents, and oxygen extraction ratio for sham (Δ), survivors (lived) (□), and nonsurvivors (died) (•). Mean ± SE. Time for last nonsurvivor value was actually time of death. *$P < 0.05$ compared with baseline. +$P < 0.05$ between Lived and Died at specified time points.

Comparison of pHm with invasive determination of acidosis

Figure 4 compares noninvasive NIRS pHm with invasive measures of acidosis: arterial (pHa) and venous (pHv) pH, along with arterial BE and blood lactate for sham, survivors (lived), and nonsurvivors (died) at the four experimental time points. There were no differences in the baseline values between sham, lived, or died within each parameter, but, as expected, the baseline pHa (7.43 ± 0.004) was significantly higher than pHv (7.39 ± 0.006). The baseline pHm (7.28 ± 0.02) was significantly lower than pHv. Arterial pH remained stable for shams and was not significantly different from the survivors and the nonsurvivors throughout the study period. There was no change in pHa as a result of shock for either surviving or nonsurviving pigs, but a small significant decrease was observed at the end of fluid resuscitation. Venous pH declined to 7.32 ± 0.01 after shock
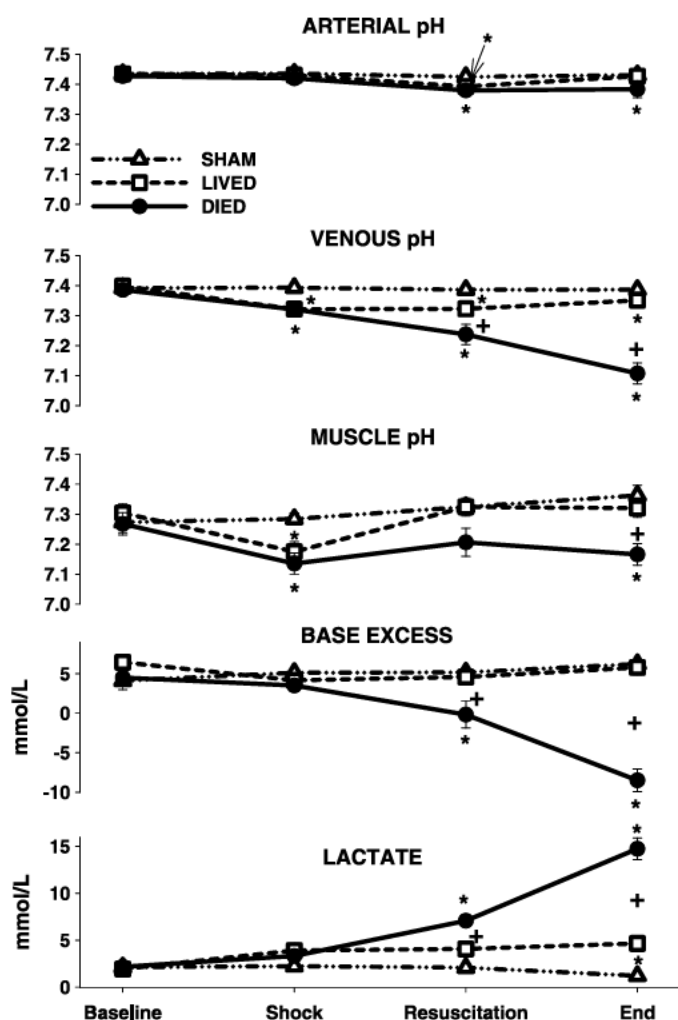
Fig. 4. Comparison of average arterial, venous, and noninvasive muscle pH, arterial base excess, and lactate for sham (△), survivors (lived) (□), and nonsurvivors (died) (•). Mean ± SE. Time for last nonsurvivor value was actually time of death. *$P < 0.05$ compared with baseline. +$P < 0.05$ between Lived and Died at specified time points.

for both lived and died, but, at the end of resuscitation, pHv for nonsurvivors (7.24 ± 0.03) was significantly less than for survivors (7.32 ± 0.03, $P < 0.001$). Venous pH continued to improve for survivors but got worse for the nonsurvivors. Muscle pH decreased to less than 7.20 as a result of shock for both the lived and died groups. At the end of resuscitation, pHm returned to baseline for survivors and increased slightly for nonsurvivors. Muscle pH for survivors at the end was significantly different from that of nonsurvivors ($P < 0.05$). Muscle pH was lower than pHv at resuscitation for both lived (pHv, 7.32 ± 0.02; pHm, 7.18 ± 0.03) and died (pHv, 7.32 ± 0.01; pHm, 7.14 ± 0.04). Both pHv and pHm rose at the end (pHv, 7.35 ± 0.02; pHm, 7.32 ± 0.03) in survivors but fell in nonsurvivors at the end (pHv, 7.11 ± 0.04; pHm, 7.17 ± 0.04).

There was no change in BE in the shams or the surviving pigs during the course of the study and the values in survivors remained similar to shams. Base excess decreased significantly after resuscitation and the end for nonsurvivors and was lower than those for both survivors and shams. The lactate rose slightly in response to shock for pigs in both the lived and died groups, but this elevation was not significant. Lactate in the nonsurvivors

continued to increase to significantly higher levels than survivors after resuscitation and rose to very high levels at the end.

Time response of noninvasive measurements

The CareGuide makes measurements continuously, so we explored the rapidity of the changes in SmO₂ and pHm induced by hemorrhage and resuscitation before any animals died. Figure 5 shows the concomitant changes in the major hemodynamic changes every 5 min with the changes in SmO₂ and pHm. Changes in SmO₂ and pHm did not become significant until near the completion of the controlled hemorrhage, which was 34% of the estimated blood volume. There were no differences in any of the hemodynamic and CareGuide variables between survivors and nonsurvivors throughout the shock period, indicating that the degree and timing of the induced shock were similar between both groups of animals. There was significantly more blood loss for the nonsurvivors after resuscitation was complete. The trend in SmO₂ and pHm paralleled the changes in the hemodynamic variables during resuscitation and became significantly different between survivors and nonsurvivors at 60 min, when all resuscitation fluid was delivered.

DISCUSSION

This study evaluated the response of noninvasively determined pHm and SmO₂ in a swine shock model that significantly lowered oxygen delivery followed with uncontrolled hemorrhage induced by splenic injury. Response of the noninvasive parameters was further evaluated as the animals were resuscitated with restricted volumes of fluid. It was shown that, for both pH and SO₂, venous and muscle values were similar to each other at the end of resuscitation for both surviving and nonsurviving animals. The pH and SO₂, venous and muscle, significantly declined as a result of bleeding, but lactate and BE did not show significant changes despite the decrease in oxygen delivery. Only during resuscitation did the blood measures of acidosis indicate the mismatch between available oxygen and the metabolic needs of the tissue. When the continuous data were analyzed in 5-min increments, noninvasive pHm and SmO₂ tracked the adequacy of resuscitation in real time, indicating at the time all fluid was delivered, which animals would live and which would die.

This study was not designed to investigate the effectiveness of pHm and SmO₂ in successfully guiding resuscitation. It was shown here that pigs that later died had significantly lower SmO₂ and pHm than pigs that survived. The implication is that, if resuscitation was actively guided with either parameter, those pigs which had low pHm and SmO₂ would have been given additional fluid and potentially would have survived. Xu et al. (13) have shown in a swine shock model that successful fluid resuscitation can be guided with sublingual PCO₂ measurements, another method for assessing tissue acidosis.

Venous pH and pHm were different from each other at the end of shock but were similar in value at resuscitation. We previously observed this in a severe swine shock model after 15 min of bleeding, where we measured tissue pH of the liver and venous pH from the hepatic vein (14). In both protocols, there was a rapid and significant drop in oxygen delivery. Using invasive
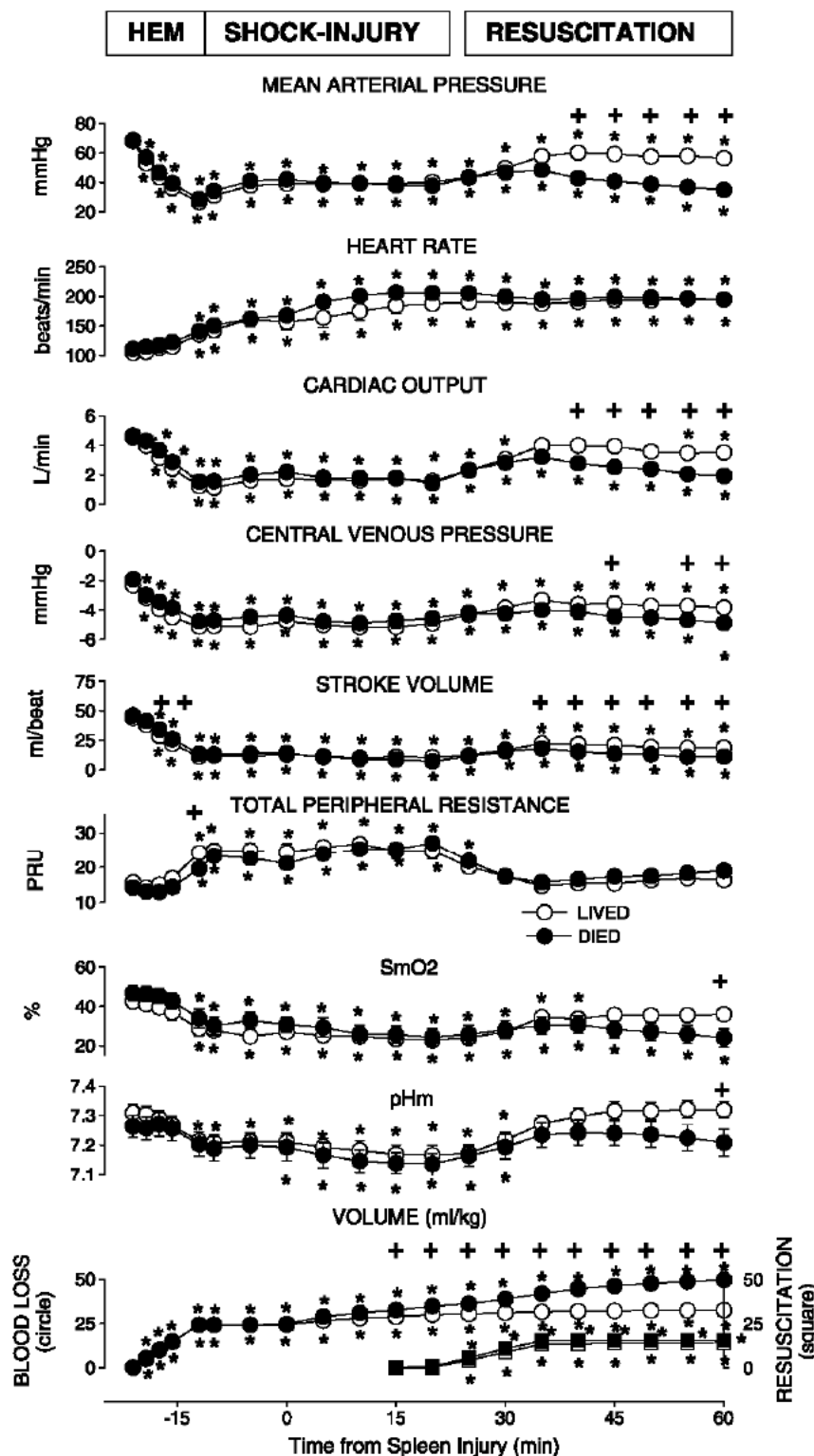
FIG. 5. Early time-course changes in mean arterial pressure, heart rate, cardiac output, central venous pressure, stoke volume, total peripheral resistance, noninvasive SmO₂, and pHm, with total hemorrhage and resuscitation volumes for survivors (lived) (□) and nonsurvivors (died) (•). Mean ± SE. *$P < 0.05$ compared with baseline. +$P < 0.05$ between lived and died at specified time points. From 20 to 12 min was the time of 24 mL/kg controlled hemorrhage (HEM). From 12 to +15 min was the time of shock and spleen uncontrolled hemorrhage from the spleen injury induced at time 0. From +15 to 60 min includes the response to resuscitation before any of the animals died.

sensors in the liver, we have previously shown that the drop in tissue (interstitial fluid) pH occurred very rapidly (15). In shock, hydrogen ions are produced in the cells and are transported through the interstitial fluid to the blood. The interstitial fluid is in equilibrium with the capillaries. The NIRS-based pHm measurement is an indication of the interstitial fluid pH in a local region of tissue and showed a more rapid accumulation of hydrogen ions compared with pHv, which is more representative of systemic acid levels. Across time, regional and systemic levels of acidosis seemed to equilibrate.

Interstitial muscle pH and PCO_2 were measured directly by Clavijo-Alvarez et al. (16) in a swine model of decompensated shock and resuscitation using invasive sensors implanted into the skeletal muscle. In their study, pHm decreased, on average, to a lower value than our noninvasive pHm measurement probably because of the prolonged shock time (>100 min) before resuscitation in their fixed pressure model of shock compared with our approximately 30-min shock period before resuscitation.

Figure 4 shows how the trends in lactate and BE compare with arterial, venous, and muscle pH. The lactate and BE showed small nonsignificant rises at the 15-min time when there had already been considerable blood loss and shock that resulted in significant changes in pHv and pHm. With longer periods of hemorrhage, lactate and BE change significantly (14, 16, 17). In our model simulating rapid response to hemorrhage, lactate and BE do not provide real-time information about ongoing blood loss. It has been suggested that BE and, to some extent, lactate are good predictors of mortality from trauma because they represent the accumulated oxygen debt resulting from the mismatch between oxygen delivery and demand (18). It is possible that not only does acidosis need to be prolonged but that there needs to be delivery of resuscitation fluid to wash accumulated metabolites into the blood to be detected via blood sampling for BE and lactate.

The SmO_2 and pHm provided similar information as their venous counterparts at the end of resuscitation. The rapidity of the SmO_2 and pHm responses to worsening shock and in response to resuscitation can be seen in Figure 5. When blood loss stabilized to less than 50% estimated blood volume in survivors, the SmO_2 and pHm stabilized. However, as occult bleeding continued in nonsurvivors to values greater than 50% of the estimated blood volume (i.e., >35 mL/kg), the trend for the SmO_2 and pHm reflected the poor status of the animal as quickly as the more invasive parameters of SBP and CO. The SmO_2 provided an early and ongoing indication of the reduction in oxygen delivery, similar to that observed in other studies measuring StO_2 (6, 7). Through the simultaneous measurement of pHm, we could also determine when available oxygen was insufficient. For survivors, although SmO_2 was still low, pHm returned to baseline, indicating that oxygen that was delivered was adequate to meet metabolic demand. While BE and lactate may represent the accumulated oxygen debt, pHm may indicate ongoing mismatch and may help prevent the delivery of too much resuscitation fluid.

A limitation of this study is that it was performed in anesthetized animals, a requirement for being able to perform an uncontrolled parenchymal hemorrhage mimicking noncompressible bleeding, as is common in today's combat injuries. We expected the baseline SmO_2 to be more similar to the SvO_2, as Ward et al. (19) found in conscious humans undergoing lower body negative pressure; here, we observed a range of baseline SmO_2 (18%–64%). We suspect that the low levels observed on a few animals may be an artifact of the surgical preparation. However, the responses of the SmO_2 in these animals showed parallel trends for the most part either increasing values for survivors or decreasing values for nonsurvivors after resuscitation. In the current study, the most consistent response was the trend. For the nonsurvivors, most showed a downward trend (seven of

13) or no change (five of 13), with only one animal having a very small increase. In contrast, 10 of 13 of the surviving animals showed an upward trend, two showed no change, whereas only one showed a small decrease.

It is noted that when the statistical analysis included the sham group and time points were limited to the four times where blood values were measured, SmO_2 and pHm were not significant between survivors and nonsurvivors at the end of resuscitation (Figs. 3 and 4). However, when data were analyzed every 5 min during shock and resuscitation and survivors and nonsurvivors were compared directly, both SmO_2 and pHm indicated significantly lower values for nonsurvivors (Fig. 5). It is suggested that the analysis including the shams at only four time points may have been underpowered, and that data in Figure 5 are more representative of actual clinical use where the value of monitoring is real-time assessment of the patient.

Muscle pH and SmO_2 can be noninvasively and continuously measured in a prehospital setting because the sensor is rapidly placed on the patient's skin and provides information in less than 30 s. Muscle pH and SmO_2 tracked hemodynamic parameters that are currently measured continuously within the hospital (MAP, CO) to assess the onset of shock but are not available during air or ground transport. Muscle pH provided a sensitive, noninvasive, real-time indication of tissue acidosis that was responsive to the adequacy of resuscitation to meet metabolic demand (end-organ perfusion).

This swine study characterized the response of a novel noninvasive sensor that simultaneously and continuously determined pHm and SmO_2. The pHm measurement continuously assesses trends in acidosis and has the potential to provide continuous real-time feedback on the adequacy of resuscitation to assure sufficient end-organ perfusion. These results suggest that further study on trauma patients is warranted particularly for use in the prehospital setting.

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